Neuropsychologia 50 (2012) 3721–3728

Contents lists available at SciVerse ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Associative recognition in mild cognitive impairment: Relationship to hippocampal volume and apolipoprotein E ☆

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ARTICLE INFO

Article history:
Received 20 January 2012
Received in revised form
16 October 2012
Accepted 19 October 2012
Available online 24 October 2012

Keywords:
Mild cognitive impairment
Associative memory
Hippocampus
Apolipoprotein E

ABSTRACT

Associative memory involves remembering relations between items of information and is critically dependent on the hippocampus, a brain structure that shows early changes in amnestic mild cognitive impairment (aMCI) and Alzheimer's disease. We examined associative and item memory in aMCI with a focus on the role of medial-temporal lobe regions and genetic risk for Alzheimer's disease. Twenty-four individuals with aMCI and 21 demographically matched healthy older adults underwent associative recognition testing, structural brain imaging, and apolipoprotein E (ApoE) genotyping. A significant interaction between group and recognition type indicated poorer associative recognition than item recognition across tasks in the aMCI group relative to controls. Within the aMCI group, associative but not item recognition showed sizable and significant correlations with hippocampal volume (but not with other medial temporal-lobe structures) and with number of ApoE ε4 alleles. Correlations were smaller and generally not significant in the control group. Our findings replicate and extend previous studies by showing an associative recognition impairment in aMCI that is not accounted for by an item recognition deficit, is related to structural integrity of the hippocampus, and increases with genetic risk for Alzheimer's disease.

1. Introduction

In recent years, there has been increased interest in studying the cognitive profiles that characterize amnestic mild cognitive impairment (aMCI). Because aMCI is a known risk factor for Alzheimer's dementia (AD; Petersen et al., 1999), understanding the cognitive pattern associated with aMCI provides insight into the earliest changes of incipient AD. One of the defining characteristics of aMCI is the presence of memory decline that is greater than normally expected for age. However, the specific memory processes and systems affected by aMCI are not entirely known. Much of what we know about memory in aMCI comes from studies using traditional clinical tests that measure memory for recently presented items such as word lists, prose passages, or geometric figures (e.g., Bäckman, Jones, Berger, Laukka, & Small, 2005; Collie & Maruff, 2000; Greenaway, Lacritz, Binegar, Weiner, Lipton, & Cullum, 2006).

There has been more limited study of additional memory changes in aMCI, and this area of research is beginning to provide a broader understanding of the cognitive and neural mechanisms that underlie aMCI. Recent studies have shown, for example, that aMCI is also associated with impairments in prospective memory (e.g., Blanco-Campal, Coen, Lawlor, Walsh, & Burke, 2009; Karantzoulis, Troyer, & Rich, 2009; Troyer & Murphy, 2007), autobiographical memory (Irish, Lawlor, O'Mara, & Coen, 2010; Leyhe, Muller, Eschweiler, & Saur, 2010; Leyhe, Muller, Milian, Eschweiler, & Saur, 2009; Murphy, Troyer, Levine, & Moscovitch, 2008), semantic memory (Estévez-González et al., 2004), and working memory (Gagnon & Belleville, 2011). These findings underscore involvement of a broad range of neural networks in

☆ This research was funded by a grant from the Alzheimer Society of Canada. We would like to acknowledge the assistance of Dr. James Kennedy for genetic analysis, Dr. Mallar Chakravarty for intracranial volume measurement, Rotman Research Institute's Imaging Lab for MRI acquisition and management, and Alyssa Borders and Andy Yonelinas for PDP calculations.

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http://dx.doi.org/10.1016/j.neuropsychologia.2012.10.018

the memory profile that characterizes aMCI. In the current study, we examine another type of memory that has not been well studied in aMCI to date – associative memory – with a focus on the role of AD-related neural and genetic factors in contributing to this memory deficit in aMCI.

Associative memory involves remembering *relations* between items of information, such as remembering words that were paired together or remembering objects and their locations. Associative memory contrasts with item memory, which involves remembering individual items, such as words or objects, independent of any other information associated with them at acquisition. Direct comparisons of these two types of memory indicate that the hippocampus is more critically involved in associative than item memory. For example, studies of patients with selective hippocampal lesions have shown impairment in some types of associative recognition in the context of relative preservation of item recognition (Mayes et al., 2004; Turriziani, Fadda, Caltagirone, & Carlesimo, 2004). Similarly, functional neuroimaging studies have shown that, although hippocampal regions are active during recognition of both item and associative information, the hippocampal response is greater during associative recognition (Davachi & Wagner, 2002; Yonelinas, Hopfinger, Buonocore, Kroll, & Baynes, 2001).

Because some of the earliest neuropathological changes in aMCI and early AD occur in the hippocampus (reviewed in Masdeu, Zubieta, & Arbizu, 2005), it is not surprising that individuals with these cognitive disorders are indeed impaired on associative memory tasks such as remembering word pairs, pattern-location pairs, and object-action pairs (Atienza, Atalaia-Silva, Gonzalez-Escamilla, Gil-Neciga, Suarez-Gonzalez, & Cantero, 2011; Collie, Myers, Schnirman, Wood, & Maruff, 2002; Duchek, Cheney, Ferraro, & Storandt, 1991; Irish, Lawlor, Coen, & O'Mara, 2011; Karantzoulis, Rich, & Mangels, 2006; Storandt & Hill, 1989). However, recognition of pairs involves not only associative memory but also item memory, because in order to remember associations between items, one must also remember the items themselves. Consequently, to examine memory for associations per se, it is necessary to compare it directly with memory for the individual items. We have done this in our previous aMCI research (Troyer et al., 2008), in which we derived both item and associative recall measures from the same memory trials, using symbol–symbol and figure-location stimuli from standard clinical tests (i.e., Digit Symbol subtest of the Wechsler Adult Intelligence Scale-3, Wechsler, 1997; Brief Visuospatial Memory Test–Revised Benedict, 1997). To account for differences in item recall, we calculated average associative recall scores that included only the items that were correctly recalled. Using these methods, we found an associative-memory impairment in aMCI that was significantly greater than that seen in healthy participants even after controlling for item memory. Similarly, others have found that, relative to healthy aging, aMCI was associated with more impaired associative than item memory for words paired with a prior context (i.e., auditory or visual presentation; Anderson et al., 2008) and words paired with cue types (i.e., letter or category cues; Hanseeuw, Dricot, Kavec, Grandin, Seron, & Ivanoiu, 2011).

Because of the importance of studying associative memory in aMCI as a possible measure of early cognitive decline, research is needed to determine the scope and reliability of the associative memory impairment in this population. There is evidence that associative memory performance can depend on the nature of the associations that are formed. That is, within-domain associations (formed between the same or similar types of information) are less affected than between-domain associations (formed between dissimilar types of information that differ in sensory modality or spatial-temporal context) in normal aging (Troyer, D'Souza, Vandermorris, & Murphy, 2011) and amnesia (Mayes et al., 2004; Vargha-Khadem et al., 1997). In the present study, we examined memory for both types of associations – using word–word and face-name pairs, respectively – to determine whether an associative memory deficit is present and whether the extent of the deficit depends on the type of association. To enable us to examine item and associative memory separately, we applied process dissociation analytical methodology (described subsequently) to obtain estimates of the independent contributions of item and associative memory during pair recognition.

In addition, we aimed to further our understanding of the biological underpinnings of the associative memory deficit in aMCI by examining its relationship with regional volumes of critical brain structures as well as its association with genetic risk for AD. Our regional brain analyses focused on volumetric measures of the hippocampus and related medial temporal-lobe structures. These regions were selected based on previous findings showing the critical importance of the hippocampus in associative memory in healthy adults and those with amnesia (e.g., Davachi & Wagner, 2002; Mayes et al., 2004; Turriziani et al., 2004; Yonelinas et al., 2001) as well as emerging evidence that atrophy in the hippocampus is related to associative memory impairment in aMCI (Ateinza et al., 2011; Hanseeuw et al., 2011). We were interested in the total hippocampal volume in general and the posterior hippocampus specifically. The latter is based on findings of greater atrophy in posterior than anterior hippocampal regions in early AD (Scher et al., 2007; Wolf et al., 2001), as well as behavioral evidence that successful encoding of episodic information engages the posterior but not anterior hippocampus (Fernández et al., 1998), and the size of the posterior hippocampus, and its ratio with anterior hippocampus, is predictive of recollective memory in young adults (Poppenk & Moscovitch, 2011).

We also related associative memory performance to genetic risk for AD, as measured by apolipoprotein E (ApoE) genotype. The presence of an ApoE ε4 allele is known to be associated with a higher risk of future AD among both individuals who are cognitively normal at baseline (e.g., Corder et al., 1993; Farrer et al., 1997) and those with aMCI (e.g., Aggarwal et al., 2005; Tierney et al., 1996). Furthermore, ε4 is associated with atrophy in the hippocampus and the entorhinal cortex (Farlow et al., 2004; Juottonen, Lehtovirta, Helisalmi, Riekkinen, & Soininen, 1998) and is related to poorer memory ability on clinical tests of paragraph and list learning in aMCI (e.g., Farlow et al., 2004; Levy et al., 2004). Given these findings, it is possible that hippocampal loss related to ApoE drives the associative memory deficit in aMCI.

1.1. Summary of research goals

We examined associative recognition in individuals with aMCI and demographically matched control participants, using well-matched stimuli that allowed for testing recognition of associations for all item pairs presented for study. Because recognition of pairs involves both item and associative memory, we used methodology that allowed us to calculate separate measures of these memory types. As our primary hypothesis, we expected to find a pattern of greater impairment in associative than item recognition in the aMCI group relative to the control group. To further understand the nature of the expected associative memory deficit in aMCI, we examined consistency of findings across stimulus types, with the expectation that a between-domain face-name task would be even more sensitive to aMCI-related brain changes than a within-domain word–word task. We also examined relationships between associative recognition, medial-temporal-lobe structural volumes, and ApoE genotype. We expected associative recognition to be positively related to hippocampal volume and negatively related to number of ApoE ε4 alleles.

2. Methods

2.1. Participants

Participants were individuals with single-domain aMCI and matched controls with age-normal memory ability. All participants were screened by clinical interview for medical and psychiatric disorders, medications affecting cognition, and substance use. Participants were also screened for current mood symptomatology using a self-report questionnaire (i.e., Hospital Anxiety and Depression Scale, HADS; Snaith & Zigmond, 1994).

The aMCI group consisted of 24 individuals recruited from clinical referrals ($n=14$) and from the community (i.e., via newspaper advertisements and community talks, $n=10$). Diagnosis of aMCI was done according to well-established criteria (Knopman et al., 2003). That is, all participants had a *subjective memory complaint*, as determined from structured clinical interview. Evidence of an *objective memory impairment* was obtained by cognitive testing with the Hopkins Verbal Learning Test-Revised (Brandt & Benedict, 2001), Brief Visuospatial Memory Test-Revised (Benedict, 1997), Rey-Osterreith Complex Figure recall (Spreen & Strauss, 1998), and Digit Symbol incidental recall (Wechsler, 1997). We required that scores on at least two memory tests be lower than expected for the individual's age, education, and verbal IQ as estimated by expressive vocabulary performance (Wechsler, 1997). *Normal general cognitive functioning* was confirmed by age-normal scores on the Mini-Mental State Examination (MMSE; Folstein, Folstein, & Fanjiang, 2000), Digit Span (Wechsler, 1997), Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), Rey-Osterreith Complex Figure copy (Spreen & Strauss, 1998), and Trail Making Test switching (Delis, Kaplan, & Kramer, 2001). Participants had *no substantial interference* with normal daily activities, as determined from structured interviews with the individual and with a family member whenever possible. In addition, a careful review of each participant's background information, current medical conditions, self-reported mood, and the cognitive assessment were used to ascertain that no medical or psychiatric condition (other than possible incipient Alzheimer's disease) accounted for the memory impairment.

The healthy control group consisted of 21 individuals recruited from community talks, a research pool at Baycrest, and newspaper advertisements. Controls were required to obtain age-normal scores on all memory and non-memory cognitive tasks (as listed previously for aMCI screening), and to report no functional difficulty with normal daily activities.

Descriptive demographic and selected cognitive variables from the two participant groups are presented in Table 1. There were no significant group differences in age, $t(43)=-1.49$, $p=.14$, education, $t(43)=0.10$, $p=.92$, sex, $\chi^2(1, N=45)=0.13$, $p=.71$, or handedness, $\chi^2(1, N=45)=0.03$, $p=.86$. Both groups obtained normal mood scores on the HADS, with no significant group differences in endorsed symptoms of anxiety, $t(43)=-1.03$, $p=.31$, or depression, $t(43)=-0.99$, $p=.33$. As expected based on the group definitions, the aMCI group performed more poorly than the control group on all memory tests, all t's >3.5, p's $<.01$. In comparison to normative data, mean memory scores in the aMCI group were well below average (i.e., approximately 1 to 1.5 standard deviations below the mean for their age, and more than 2 standard deviations below their verbal IQ estimates). In the control group, mean memory scores were average (i.e., slightly higher than the mean for their age and within 1 standard deviation of their verbal IQ estimates). On the other cognitive tests, both the aMCI and control groups scored well within the normal range for their age and neither group was clinically impaired. There were no group differences on Vocabulary, Digit Span, or Boston Naming, all t's <1.5, p's $>.15$, and there were group differences favoring the controls on the MMSE, $t(42)=4.15$, $p<.01$, Rey-Osterreith copy, $t(43)=2.25$, $p=.03$, and Trail Making Test switching, $t(43)=4.17$, $p<.01$.

Table 1
Participant demographics and descriptive cognitive variables.

	aMCI ($n=24$)		Control ($n=21$)		
	Mean	(SD)	Mean	(SD)	*d*
Demographics and mood					
Age	76.1	(7.6)	72.9	(6.7)	0.5
Education years	14.2	(2.5)	14.3	(2.6)	0.0
Sex ratio (Female: Male)		15: 9		12: 9	
Handedness (Right: Left)		21: 3		18: 3	
HADS anxiety score	4.2	(2.6)	4.2	(2.6)	0.3
HADS depression score	3.0	(2.6)	2.3	(1.3)	0.3
General and non-memory cognitive tests					
MMSE score	27.4	(1.8)	29.1	(0.9)	1.2*
Vocabulary SS	14.9	(1.9)	14.9	(2.5)	0.0
Digit Span SS	12.1	(2.1)	12.2	(2.6)	0.1
Boston Naming Test SS	10.3	(3.1)	11.4	(2.5)	0.4
Rey-Osterreith figure copy SS	9.1	(1.5)	10.2	(1.7)	0.7
Trail Making Test switching SS	10.6	(1.9)	12.8	(1.6)	1.3*
Selected memory tests					
HVLT-R immediate recall SS	7.8	(2.6)	12.1	(1.8)	1.9*
HVLT-R delayed recall SS	5.6	(3.6)	12.2	(1.1)	2.5*
BVMT-R immediate recall SS	5.9	(2.3)	11.4	(2.0)	2.6*
BVMT-R delayed recall SS	6.2	(2.8)	11.5	(1.6)	2.3*

Note. aMCI=amnestic mild cognitive impairment; *d*=Cohen's measure of effect size; HADS=Hospital Anxiety and Depression Scale; MMSE=Mini-Mental State Examination; SS=scaled score based on age-corrected normative data; HVLT-R=Hopkins Verbal Learning Test-Revised; BVMT-R=Brief Visual Spatial Memory Test-Revised.

* Group differences $p<.01$.

2.2. Associative recognition tasks

We created two associative recognition tests with procedures modeled after those of Mayes et al. (2004). As described subsequently, the number of items presented and the exposure durations differed between the tasks and were selected to avoid floor and ceiling effects and to balance level of difficulty, based on pilot testing. Two presentation trials were administered for each task because our previous research (Troyer et al., 2008) indicated that item/association differences increased after repeated learning trials. To minimize primacy and recency effects, the first two and last two presentation items were excluded from recognition testing. Six versions of each task were created so that each item was included equally often in each test condition (i.e., intact, new, or recombined; see subsequent task descriptions). Use of task versions and order of administration of the two recognition tasks were counterbalanced across participants.

2.2.1. Word–word association test

Stimuli were generated from an electronic database of words (Coltheart, 1981) and consisted of nouns, verbs, and adjectives containing 3 to 8 letters. A total of 52 semantically unrelated word pairs were created. Four word pairs were used as primacy and recency items, and the remaining 48 were test items. The 48 word pairs were divided into three lists of 16 items each: word pairs from two lists were presented for study, and these plus the word pairs from the third list were used for recognition testing. The words composing the three lists did not differ in concreteness (Paivio, Yuille, & Madigan, 1968), frequency (Thorndike & Lorge, 1944), or number of letters.

Word pairs were presented visually on a computer screen. In the study phase, 36 word pairs (4 primacy/recency pairs and 32 target word pairs) were presented for 3 s each with a 0.5 s inter-stimulus interval. After all word pairs were presented once, there was a brief delay to provide instructions, and then the same word pairs were presented again in a different order. Following the second presentation, there was a 30-s delay during which instructions were provided for recognition testing. The recognition test consisted of 48 word pairs presented individually in a pseudo-random order, including 16 intact (old) word pairs previously presented together, 16 recombined pairs consisting of old words that were not previously presented together, and 16 new word pairs that were not previously presented. For each test item, participants were instructed to press a key labeled "yes" if the stimulus pair was presented previously (i.e., an intact pair) and press "no" if it was not (i.e., a recombined or new pair). The recognition test was self-paced. At the conclusion of recognition testing, the examiner asked participants to state the instructions regarding when to press "yes" or "no" in order to confirm that they followed the correct procedures.

2.2.2. Face-name association test

Black-and-white images of faces (half male and half female) were taken from the Nottingham scans (University of Stirling (n.d.), 2005). First names were taken from a listing of the most common baby names for each decade (Social Security Administration, 2005). A total of 28 face-name pairs were created by randomly pairing gender-appropriate names with faces. Presentation stimuli included 20 pairs: four primacy and recency items, and 16 test items. During the study phase, the 20 faces were presented individually on the computer screen for 6 s each with an inter-stimulus interval of 0.5 s; corresponding names were presented orally through the computer speaker while the face was exposed. The same procedures were used as for the previous task, with two list presentations, a 30 s delay, yes/no recognition testing, and procedural checking. The recognition test consisted of 24 face/name pairs, including 8 intact pairs, 8 recombined pairs, and 8 new pairs.

2.2.3. Calculation of memory scores

For each task, raw data were the proportions of items endorsed (i.e., received a "yes" response) for each type of recognition probe (i.e., intact, recombined, and new). We examined the relative contributions of item (I) and associative (A) memory processes to performance on each task by applying the logic of process dissociation (Jacoby, 1991), which assumes that I and A contribute independently to recognition of intact and recombined pairs. On this assumption, correct recognition of intact pairs depends on the contribution of A plus I in the

absence of A, that is I(1 − A). False alarms to recombined pairs reflect a contribution from I processes in the absence of A only; thus, p(yes|Intact)=A+I(1 − A) and p(yes|Recombined)=I(1 − A). It therefore follows that an estimate of A can be derived as the difference of these proportions: yes|Intact—yes|Recombined. For our estimate of item memory, we used a dual-process signal-detection model, which adjusted for individual differences in response bias (Yonelinas, Regehr, & Jacoby, 1995; for a similar application of this approach, see Wolk, Signoff, & DeKosky, 2008). These d' estimates were obtained using PDPSolve.xls (downloaded from http://psychology.ucdavis.edu/Labs/Yonelinas/).

2.3. Neuroimaging

Scanning was performed on a 3.0-T Siemens Magnetom Tim Trio scanner (AG, Erlangen Germany) with a matrix 12 channel head coil. High-resolution anatomic images were obtained using T1-weighted, MP-RAGE sequence (TR=2000 ms, TE=2.63 ms, T1=1100 ms, flip angle 9°, 256 × 192 acquisition matrix, 160 slices, slice thickness of 1.0 mm, and a NEX=1 with a skip of 0.0 mm). A T2-weighted Fluid Attenuated Inversion Recovery sequence (TR=9000 ms, TE=96 ms, T1=2200 ms, flip angle 165°, 256 × 162 acquisition matrix, 30 slices, slice thickness of 5.0 mm, NEX=1) was added to rule out brain lesions. All head rotations were corrected using oblique imaging in the axial plane.

Images were reconstructed using AFNI software (Cox, 1996). Manual tracings were completed by a rater (A.M.) blind to subject diagnosis and trained by F.G. in using the ROI module of Analyze AVW™ version 10.0 software (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN) on non-normalized T1-weighted images.

For tracing medial temporal lobe (MTL) structures, we used protocols described previously for the hippocampus and the parahipocampal gyrus (Rosenbaum et al., 2008; Weiss, DeWitt, Goff, Ditman, & Heckers, 2005) and for the entorhinal and perirhinal cortex (Insausti et al., 1998), with the exception that we traced every slice rather than every second slice in order to increase the sensitivity of our measurements. Hippocampal tracings were made on sagittal slices beginning with the first lateral slice where the hippocampal grey matter could be clearly detected and moving medially until both the anterior and posterior hippocampus could no longer be delineated. The hippocampal tracings included the hippocampus proper, subiculum, fimbria, alveus, and the dentate gyrus. The hippocampus was further divided into two subregions on coronal slices: the anterior hippocampus consisted of the uncus, and the posterior hippocampus consisted of the hippocampal body and tail. Parahippocampal tracings were made on coronal slices beginning on the first slice posterior to perirhinal cortex and continued until the crux of the fornix appeared. Entorhinal cortex tracings began two sections posterior to the limen insulae and ended at the level of the gyrus intralimbicus. The medial border of the entorhinal cortex was defined as the ventral border of the gyrus semiannularis. The lateral border of the entorhinal cortex was defined as the medial bank of the collateral sulcus if it was judged to be of regular depth (1–1.5 cm in length). If the collateral sulcus was shallow (< 1 cm) then the lateral border of the entorhinal cortex was defined as the fundus of the collateral sulcus, and if the collateral sulcus was considered to be deep (≥ 1.5 cm) then the lateral border was defined as the medial edge of the collateral sulcus. The perirhinal cortex was traced coronally beginning 2 slices anterior to the limen insulae and ending one slice posterior to the entorhinal cortex. The medial border of the perirhinal cortex was defined as the lateral border of the entorhinal cortex, and the lateral border of the perirhinal cortex was defined as the lateral bank of the collateral sulcus.

Volumes of MTL structures were corrected for individual differences in head size using total intracranial volumes (TIV) calculated for each individual. Images were normalized using the ANIMAL algorithm (Collins, Holmes, Peters, & Evans, 1995) to register the images to the ICBM 152 template. Using the inverse nonlinear transformation, the newly created mask was then re-sampled to its original space, that is, to the participant's structural components, and the resulting voxels were summed. The TIVs were then averaged to create a mean TIV that was multiplied by the non-normalized volume and divided by the participant's TIV to yield the corrected volume.

To determine consistency in tracing these protocols, 5 scans were randomly chosen for retracing after the initial tracing was completed on all scans. A Pearson correlation on the total traced volumes showed high intra-rater reliability, $r(5)=.95$, $p < .01$. Correlations for individual MTL structures were all .85 or higher, with the exception of the right entorhinal and perirhinal cortices, which were .58 and .62, respectively.

Three aMCI participants were unable to undergo neuroimaging because of medical contraindications for MRI. Scans that were acquired for 2 additional participants (1 aMCI and 1 control) were inadvertently lost prior to analysis. Thus, there were 40 participants (20 aMCI and 20 control) with MRI data.

2.4. Genotyping

ApoE genotyping was done using methods described by Hixson and Vernier (1990) and assay systems developed by Koch et al. (2002). Genotype was deduced by observers blind to participant classification as aMCI or healthy control. For subsequent analyses, the independent variable recorded for each participant was the number of ε4 alleles in their genotype: 0 for individuals with genotypes ε2/ε2, ε2/ε3, or ε3/ε3, 1 for genotypes ε2/ε4 or ε3/ε4, and 2 for genotype ε4/ε4.

2.5. Data analyses

We conducted a 2 × 2 × 2 repeated measures MANOVA with recognition type (item vs. associative recognition) as separate within-group variables, stimulus type (word–word vs. face-name) as within-group repeated-measures variables, and group membership (aMCI vs. control) as a between-group variable. To examine interactions, we calculated standardized scores based on the control group means and standard deviations (Wolk et al., 2008) and tested for group differences on associative vs. item recognition (i.e., a two-way interaction), and recognition-type differences between the face-name and word–word tasks (i.e., a three-way interaction). To examine relationships with brain volumes and genotype, we conducted correlations between these variables and the four recognition measures. We used parametric correlation analyses (i.e., Pearson's r) for the continuous variable of MTL structural volume and nonparametric correlation analyses (i.e., Spearman's ρ) for the ordinal variable of number of ApoE ε4 alleles.

3. Results

3.1. Item and associative recognition

Estimates of item and associative recognition are shown in Fig. 1. Repeated-measures MANOVA revealed a main effect of group, $F(2,42)=10.27$, $p < .001$, $\eta_p^2=.33$, with the control group obtaining higher recognition scores overall. There was also a main effect of stimulus type, $F(2,42)=6.15$, $p=.005$, $\eta_p^2=.23$, but no group-by-stimulus-type interaction, $F(2,42)=1.116$, $p=.33$, $\eta_p^2=.05$, indicating that difficulty levels for the word–word and face-name tasks did not differ between the groups.

Examination of between-subjects effects revealed that, in distinguishing old and new items, the aMCI group relied on item recognition slightly more than the control group, $F(1,43)=4.24$, $p=.046$, $\eta_p^2=.09$, and relied on associative recognition considerably less, $F(1,43)=2.26$, $p < .001$, $\eta_p^2=.31$. Importantly, analysis of the standardized scores showed that, as hypothesized, there was a significant group-by-recognition-type interaction, $F(1,43)=20.30$, $p < .001$, $\eta_p^2=.32$, indicating poorer associative recognition ($z=-0.58$) than item recognition ($z=0.27$) in the aMCI group relative to controls. There was also a three-way interaction between group, stimulus type, and recognition type, $F(1,43)=4.63$, $p=.037$, $\eta_p^2=.10$, although this was not in the predicted direction. The associative memory deficit in aMCI was slightly larger for

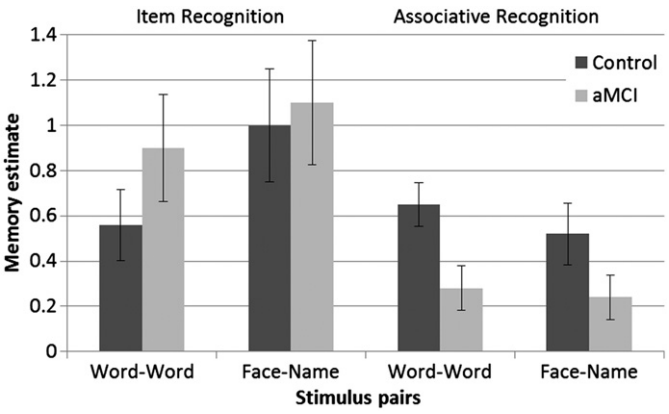

Fig. 1. Estimates of item and associative recognition of word–word and face-name pairs. The estimate of item recognition is a d' value and the estimate of associative recognition is a difference score. A two-way interaction (calculated with standardized scores) shows that amnestic mild cognitive impairment (aMCI) is associated with lower associative than item recognition. Error bars represent 95% confidence intervals.

Table 2
Medial-temporal-lobe structure volumes (mm^3).

	aMCI ($n=20$)		Control ($n=20$)		
	Mean	(SD)	Mean	(SD)	*d*
Hippocampus total	4227.5	(720.2)	5290.7	(555.9)	1.7*
Anterior	1911.3	(487.4)	2362.6	(421.0)	1.0*
Posterior	2329.2	(319.3)	2928.1	(414.1)	1.6*
Entorhinal cortex	1249.7	(328.8)	1815.6	(329.4)	1.7*
Perirhinal cortex	2893.4	(752.5)	3570.8	(624.0)	1.0*
Parahippocampal cortex	1138.4	(234.5)	1397.9	(448.7)	0.7*

Note. Volumes presented were corrected for overall intracranial volume. aMCI=amnestic mild cognitive impairment; *d*=Cohen's measure of effect size.

* Group differences $p<.05$.

Table 3
Correlations between medial-temporal-lobe structure volumes and measures of item and associative recognition on the word–word and face-name tasks.

	Item recognition		Associative recognition	
	Word–word	Face-name	Word–word	Face-name
	aMCI group ($n=20$)			
Hippocampus, total	.19	−.13	.48*	.47*
Anterior	.15	−.29	.39	.45*
Posterior	.14	.07	.43	.34
Entorhinal cortex	.00	−.11	.26	.17
Perirhinal cortex	−.15	−.20	.00	.15
Parahippocampal gyrus	−.10	.03	.25	.31
	Control group ($n=20$)			
Hippocampus, total	−.05	−.31	.29	.40
Anterior	.15	−.38	.04	.06
Posterior	−.22	−.02	.35	.48*
Entorhinal cortex	−.05	−.40	.17	.11
Perirhinal cortex	.20	−.46*	.06	−.13
Parahippocampal gyrus	−.07	.12	.06	.19

Note. Data presented are Pearson correlation coefficients. aMCI=amnestic mild cognitive impairment.

* $p<.05$.

recognizing word–word pairs ($z=-1.46$) than for face-name pairs ($z=-0.87$).

3.2. Relationship with hippocampal volumes

MTL structural volumes are presented in Table 2. There were significant group differences with large effect sizes for all of these structures, with the aMCI group showing smaller volumes of the total hippocampus, $t(38)=5.23$, $p<.01$, anterior hippocampus, $t(38)=3.13$, $p<.01$, posterior hippocampus, $t(38)=5.12$, $p<.01$, entorhinal cortex, $t(38)=5.44$, $p<.01$, perirhinal cortex $t(38)=3.10$, $p<.01$, and parahippocampal gyrus, $t(38)=2.29$, $p<.01$.

We were most interested in the relationship between hippocampal volumes and memory performance, given the role of this MTL structure in associative recognition. As seen in Table 3, in the aMCI group, correlations between total hippocampal volumes and the associative recognition measures were both medium in size and were statistically significant. A similar pattern emerged when examining the anterior and posterior hippocampus separately: all correlations with associative recognition were medium in size, although only the largest was significant with our sample size of 20. In the case of item recognition, correlations with hippocampal volumes were entirely absent, which emphasizes the specific role of this brain region in associative recognition; these correlations were small to negligible in size and were not statistically significant. Correlations between the four recognition variables and the other MTL structures were numerically smaller, generally ranged from negligible to small in size, and were not significant.

In the control group, correlations were numerically lower than in the aMCI group. Correlations between total hippocampal volume and associative recognition measures were small to medium in size but not statistically significant. Looking at the anterior and posterior hippocampus separately, only one correlation was statistically significant: the medium-sized correlation between face-name associative recognition and the posterior hippocampus. Correlations between the hippocampus and item recognition, as well as between the non-hippocampal MTL structures and the recognition measures were generally small to negligible in size and were not significant. The exception is the correlation between the perirhinal cortex and face-name item recognition, which was *negative*, medium in size, and significant.

Table 4
Apolipoprotein E (ApoE) allele distribution.

	aMCL ($n=24$)		Control ($n=21$)	
Genotype				
ε2/ε2	1	(4%)	0	(0%)
ε2/ε3	1	(4%)	5	(24%)
ε2/ε4	0	(0%)	1	(5%)
ε3/ε3	10	(42%)	9	(43%)
ε3/ε4	6	(25%)	5	(24%)
ε4/ε4	6	(25%)	1	(5%)
Number of ε4 alleles				
0	12	(50%)	14	(67%)
1	6	(25%)	6	(28%)
2	6	(25%)	1	(5%)

Note. Data are presented as the number of individuals (and percent of individuals) within each group. aMCI=amnestic mild cognitive impairment.

3.3. Relationship with ApoE genotype

ApoE allele distribution is shown in Table 4. Consistent with previous studies using similar samples (Smith et al., 1998), half of our aMCI participants and one third of controls had one or more ε4 allele. As expected, the mean number of ε4 alleles was greater in the aMCI group, $M=0.75$, than the control group, $M=0.38$, one-tailed $t(41)=1.71$, $p=.05$.

Within the aMCI group, correlations between number of ε4 alleles and scores on the recognition tasks were significant only for face-name associative recognition, Spearman's $\rho=-.43$, $n=24$, $p=.04$. This correlation was driven by the particularly low performance in the aMCI subgroup with two ε4 alleles, $M=0$, $SD=0$, relative to the subgroups with one ε4 allele, $M=0.33$, $SD=0.22$, or no ε4 alleles, $M=0.31$, $SD=0.29$. Correlations were not significant for word–word item recognition, $\rho=-.04$, $n=24$, $p=.84$, word–word associative recognition, $\rho=-.11$, $n=24$, $p=.62$, or face-name item recognition, $\rho=.31$, $n=24$, $p=.13$. In the control group, correlations between number of ε4 alleles and scores on the recognition tasks varied, $\rho's=-.31$ to .43, $n=21$, and none was statistically significant, $p's>.05$.

Relationships between genotype and structural brain volumes were also examined. In the aMCI group, number of ε4 alleles showed a large and significant correlation with total hippocampal volume, $\rho=-.50$, $n=20$, $p=.02$, and medium but non-significant correlations with the anterior hippocampus, $\rho=-.41$, $n=20$, $p=.07$, posterior hippocampus, $\rho=-.39$, $n=20$, $p=.09$, and perirhinal cortex, $\rho=-.37$, $n=20$, $p=.11$. Number of ε4 alleles was not correlated with volume of the entorhinal cortex, $\rho=-.23$, $n=20$, $p=.34$, or parahippocampal gyrus, $\rho=-.05$, $n=20$, $p=.83$. In the control group, number of ε4 alleles was not significantly related to any MTL structural volumes, $\rho's=-.37$ to .18, $n=20$, $p's>.05$.

4. Discussion

We obtained evidence that the memory impairment in aMCI is characterized by poorer associative memory than item memory. In discriminating old and new stimulus pairs, the aMCI group tended to rely more on item recognition and less on associative recognition than a matched control group. This confirms and extends previous findings using different types of stimuli. Specifically, our earlier research (Anderson et al., 2008; Troyer et al., 2008) revealed an associative-memory deficit above and beyond any item-memory deficit in aMCI when the items to be associated consisted of symbol–symbol, figure-location, and word-modality pairs. The current findings of a similar memory pattern using word–word and face-name stimulus pairs reflects the robustness of this pattern and indicates that the finding is not dependent on the particular types of information being learned.

This finding of a specific associative recognition deficit in aMCI may reflect the underlying cognitive processes thought to be involved in learning and remembering associative information. According to dual-process models, recognition memory can be supported by conscious *recollection* of items bound to their spatiotemporal context or by a more general sense of *familiarity* for the items themselves but devoid of information about their context (Jacoby, 1991; Mandler, 1980). There is evidence that, although associative recognition judgments can rely on familiarity in some situations, they are more reliant on recollection than are item recognition judgments (Yonelinas, Aly, Wang, & Koen, 2010). While our design did not permit estimation of the contributions of recollection and familiarity to item and associative memory per se, the finding of a significant associative memory deficit is consistent with other studies on single-domain aMCI that have found a significant decrement in recollection but not familiarity (Anderson et al., 2008; Serra et al., 2010). Thus, it is possible that our finding of a pronounced impairment in associative recognition relative to item recognition can be explained by an aMCI-related decrement in recollection. Other studies have found that both recollection and familiarity are comparably affected by aMCI (Algarabal et al., 2009; Ally, Gold, & Budson, 2009; Ally, McKeever, Waring, & Budson, 2009; Wolk et al., 2008) but these have all included individuals with multiple-domain aMCI. An interesting question for future research would be whether the pattern of memory findings seen here would hold in a group with multiple-domain aMCI, or whether both item and associative memory would be affected.

Our finding of a slightly greater aMCI-related associative-memory deficit in recognizing word–word than face-name pairs was unexpected. There is evidence that within-domain associations, such as those formed between word–word pairs, are mediated primarily by non-hippocampal MTL regions, whereas between-domain associations, such as those formed between face-name pairs, are mediated by the hippocampus (reviewed in Mayes, Montaldi, and Migo (2007)). Patients with focal hippocampal damage show more substantial impairment in between-domain than within-domain associative memory (Mayes et al., 2004). The cause of the discrepancy between the previous and current findings is unclear, but could be related to the different patient populations studied. It is possible that associative recognition draws on a broader set of brain structures in patients with neurodegenerative brain processes than in those with focal brain damage, and these affect associative memory in different ways. Alternatively, it is possible that differential effects are indeed present, but that we were not able to detect them using our current memory measures. Associative recognition on both tasks was poor in the aMCI group, and an examination of the raw data showed more aMCI individuals at floor-level performance (i.e., estimates of 0) on the face-name than the word–word associative recognition task. This may have artificially created larger group differences on the latter task. Further research will be useful in determining the degree and nature of the effect of aMCI on these two types of associative memory tasks. Importantly, several of our other findings, as discussed subsequently, show other differences between these associative tasks as they relate to hippocampal volumes and ApoE genotype.

Associative memory performance was strongly related to the hippocampus in the aMCI group. Hippocampal volumes showed more sizable correlations with associative recognition than item recognition across both the face-name and word–word tasks. This provides further support for the idea that the hippocampus is particularly important for remembering associative information. In the aMCI group, associative memory was related to the anterior and posterior hippocampus in a similar way. In the healthy control group, however, associative memory showed more sizeable correlations with the posterior hippocampus than the anterior hippocampus. This is consistent with previous research showing that the posterior hippocampus is particularly engaged during the successful encoding of episodic information in healthy adults (Fernández et al., 1998; Poppenk & Moscovitch, 2011).

There is less evidence for a role of other MTL structures in associative memory, as our correlations between these structural volumes and associative recognition were generally smaller in size and were not significant. Although this pattern is consistent with a large body of previous research in a number of populations, there is some evidence of involvement of the entorhinal cortex in associative memory (e.g., Atienza et al., 2011). The entorhinal cortex, like other small brain structures, are characteristically difficult to measure reliably (Price et al., 2010), and our own data showed smaller intra-rater reliability coefficients for perirhinal and entorhinal regions than other MTL regions. As such, we cannot totally rule out a contributing factor of measurement accuracy in our pattern of findings.

Similar to previous research, our groups showed the expected ApoE genotype differences, with greater incidence of the ε4 allele in the aMCI group than the control group. Moreover, in the aMCI group, the number of ε4 alleles was negatively correlated with face-name associative recognition, and this relationship was driven by the particularly poor memory performance in individuals with two ε4 alleles. The number of ε4 alleles was also related to hippocampal volumes in the aMCI group, and this may explain the relationship between ApoE genotype and some aspects of memory performance, particularly with regard to face-name pairs. These relationships could be interpreted as reflecting a higher likelihood of underlying Alzheimer's pathology in our aMCI group, in particular in the subgroup with two ε4 alleles. In a related vein, although our sample sizes and methodology preclude an examination of causal relationships, it is plausible that an increased number of ε4 alleles in individuals with aMCI results in smaller hippocampal volumes, and smaller hippocampal volumes cause poorer memory performance. This is especially evident on tasks that rely on associative recollection, such as recognition of face-name pairs. Such a correlation was not found for recognition of word–word pairs, possibly due to the hybrid nature of the latter task in which associative familiarity may play a larger role than it does for face-name pairs (Mayes et al., 2007). Thus, perhaps where associative recollection is concerned, hippocampal volume may mediate the relationship between ApoE genotype and memory performance in individuals with aMCI. Future research is necessary to determine whether the above explanation holds true.

Although a comparison of the within-domain vs. between-domain associative recognition showed unexpected differences between our groups, some of the other differences between these associative tasks were as predicted. First, although hippocampal

volumes were not generally related to memory performance in our control group, the exception was a large and significant positive correlation between the posterior hippocampus and the between-domain face-name associative measure. Likewise, only a few recognition variables had sizable relationships with ApoE genotype, and the largest of these was the significant negative correlation between number of ε4 alleles and face-name associative recognition in the aMCI group. These are isolated findings, but are nevertheless in the expected direction based on previous evidence for a prominent role of the hippocampus in between-domain associative memory and thus merit further study.

Our findings have possible implications for the clinical assessment of memory disorders. The most commonly used clinical tasks are item memory tests that measure recall or recognition of word lists, paragraphs, and geometric figures. Our findings of a disproportionate impairment in associative memory relative to item memory in aMCI underscore the need for including measures of associative memory in the clinical assessment of this population. The most sensitive tests will be those that allow examination of associative memory independent of item memory, similar to the tasks that were used in this study, given that associative memory is disproportionately impaired. Testing associative memory may be particularly well tolerated in individuals with memory concerns, because the most common self-reported memory problems in aging and in aMCI tend to involve remembering associations between items, such as faces and names or household objects and locations (e.g., Bolla, Lindgren, Bonaccorsy, & Bleecker, 1991; Frank et al., 2006; Leirer, Morrow, Sheikh, & Pariante, 1990). Thus, this type of test would have good face validity for the populations they target.

To enhance our understanding of the relationship between the hippocampus and associative memory, it would be interesting to compare associative and item memory in detecting the earliest cognitive changes in healthy individuals that eventually develop aMCI or dementia due to AD. The normal aging process is characterized by memory changes that are more pronounced for associative than item recall or recognition (e.g., Naveh-Benjamin, 2000; Troyer et al., 2011) as well as physiological changes in the MTLs and hippocampus (reviewed in Raz & Rodrigue (2006)). There are additional hippocampal changes that occur early in the course of AD, and this process may be mediated or exacerbated by the presence of ApoE ε4 alleles. Given these early brain changes, as well as our finding of poorer associative than item recognition in aMCI, it may be that tests of associative memory pick up subtle AD-related deficits before tests of item memory do. Early detection is important so that behavioral and/or pharmacological treatments to slow the progression of AD can be provided while individuals can benefit most.

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